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Diastereoselective synthesis of pyridyl substituted thiazolidin-4-ones. New ligands for the Cu(I) catalyzed asymmetric conjugate addition of diethylzinc to enones

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Abstract: Several novel thiazolidin-4-ones have been synthesized from chiral non-racemic α-mercapto acids by a three component reaction in high yields and with diastereomeric excesses up to 91%. After recrystallization, the thiazolidinones were obtained diastereomerically pure and were employed as chiral ligands in the copper catalyzed conjugate addition of diethylzinc to cyclohexenone and chalcone as model substrates. Enantioselectivities up to 62% were achieved. © 1997 Elsevier Science Ltd

Introduction

Chiral non-racemic β-amino alcohols are popular ligands in asymmetric catalysis.[1] The use of the corresponding β-amino thiols, however, has been limited due to the lack, until recently, of simple synthetic transformations to these interesting molecules. Building on the synthesis of enantiomerically pure β-amino thiols, -sulfides, and -disulfides[2] and a recently improved synthesis of both enantiomers of thiolactic acid, starting from a cheap building block, ethyl (*S*)-lactate,[3] we describe herein the synthesis and application of novel chiral thiazolidinones.

Sulfur containing compounds have been used as chiral ligands for stoichiometric[4] and catalytic enantioselective conjugate addition reactions of Grignard reagents to enones.[5–7] Furthermore, enantiomerically pure thiols and sulfides are successful catalysts in the enantioselective addition of diethylzinc to benzaldehyde.[8] Because sulfides and pyridines have a pronounced affinity for Cu(I)[9] and chiral copper catalysts have been used successfully in the enantioselective conjugate addition of dialkylzinc to enones,[10,16b] we envisioned that combination of these elements in the form of chiral thiazolidinones also might lead to ligands suited for this asymmetric transformation.

Results and discussion

Synthesis of thiazolidin-4-ones 2

Although thiazolidinones have been the subject of extensive study and diverse biological activities have been found to be associated with this class of heterocycles,[11] the elegant cyclocondensation of a mercapto acid, an amine and an aldehyde under conditions of azeotropic removal of water to give thiazolidin-4-ones is relatively unexplored.[12] The 2-pyridyl-thiazolidin-4-ones **2** are obtained in quantitative yield just by mixing α-mercapto acid, aniline, and 2-pyridinecarboxaldehyde in appropriate amounts (Scheme 1). A mixture of *cis*- and *trans*-diastereomers is produced; the former predominates (*vide infra*). No racemization of the α-mercapto acid was observed. In contrast to reactions whereby chiral amines are used (no diastereoselectivity),[12b] this synthesis using chiral α-mercapto acids proceeds with diastereomeric excesses (d.e., determined by ^{1}H NMR) varying from

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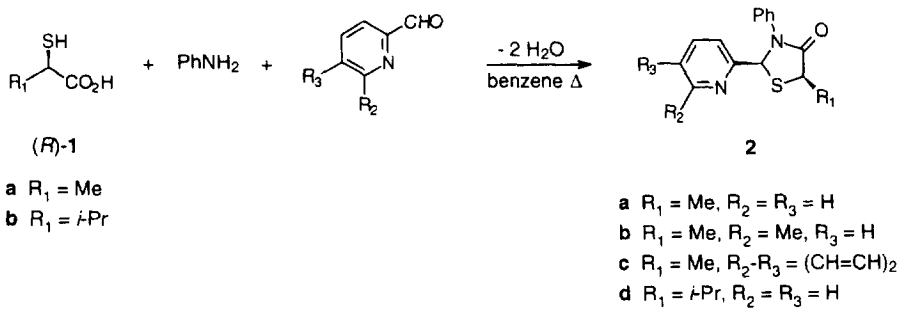
24% **2c** to 91% **2a**. No attempts were undertaken to optimize the reactions conditions in order to enhance the diastereomeric excess. Diastereomerically pure materials were obtained by simple recrystallization. In analogy to cyclocondensations of α-hydroxy acids with aldehydes[13] and other studies,[12a,c] we expected that the major isomer should have a *cis*-geometry which allows both substituents to remain in pseudo-equatorial positions. Indeed NOE experiments on **2a** confirm an interaction between hydrogens on the 2- and 5-position.



(*R*)-**1**

a R_1 = Me
b R_1 = *i*-Pr

2

a R_1 = Me, R_2 = R_3 = H
b R_1 = Me, R_2 = Me, R_3 = H
c R_1 = Me, R_2-R_3 = $(CH{=}CH)_2$
d R_1 = *i*-Pr, R_2 = R_3 = H

Scheme 1. Synthesis of thiazolidin-4-ones **2**.

Thiolactic acid, required for the synthesis of **2a–c**, was obtained as described.[3] Previously we have shown that optically active α-mercapto acids are also accessible from naturally occurring amino acids,[14] and this protocol was used for the synthesis of 2-mercapto-3-methyl-butanoic acid **1b** from *S*-valine, leading to thiazolidin-4-one **2d** (d.e. 85%). Overall, this makes these stable class of compounds easily accessible.

Application of compound 2 as chiral ligand in the copper catalyzed addition of diethylzinc to enones

First, the substituted thiazolidin-4-ones **2a–d** were examined in the CuOTf catalysed addition of diethylzinc to cyclohexenone (Table 1). With ligand **2a** (11 mol%) and 5 mol% of CuOTf a highly selective reaction to afford the 1,4-product (>95% yield, GC analysis) was found. Isolation, purification, and derivatization of the 1,4-product **4**[15] revealed an e.e. of 47% (entry 1). Sterically demanding groups on both the pyridyl group **2b** and **2c** or the α-position **2d** had an influence on the enantioselectivity. A methyl substituent at the 6-position of the pyridine ring reduces the e.e. (**2b**, 39%, entry 2), probably by inducing the formation of another aggregate of the copper complex in solution. Use of quinoline derivative **2c**, instead of pyridine, had a minor influence, whereas a sterically demanding group at the α-position in ligand **2d** gave the best results. After 2 h quantitative conversion to the 1,4-product was achieved and an enantiomeric excess of 62% was observed. This is the first example of successful copper catalyzed enantioselective conjugate addition of dialkylzinc reagents using sulfur containing ligands and the e.e. values of **4** are comparable with those found using chiral phosphorus amidites.[10,16]

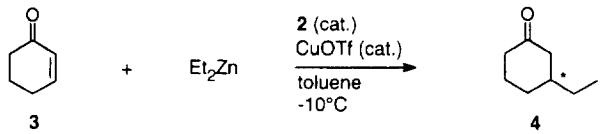
When chalcone was used as substrate these new ligands showed excellent conversions to the 1,4-product and complete regioselectivity was observed. However, enantioselectivity was low (up to 11% for **2c**). Although this class of ligands has scarcely been explored in asymmetric synthesis the results look most promising, in particular as variations in the ligand structure can easily be achieved. At this moment the optimization of the structure of this type of sulfur containing ligands is in progress. Also extension in other asymmetric transformations will be investigated.

Experimental section

General

See Ref.[18] Elemental analyses were performed in the Microanalytical Department of this laboratory.

Table 1. Enantioselective 1,4-addition of diethylzinc to cyclohexenone catalysed by CuOTf and **2**[a]



3 **4**

entry	ligand	e.e. of **4** (%)[b]	abs. conf.[c]
1	**2a**	47	*R*
2	**2b**	39	*R*
3	**2c**	49	*R*
4	**2d**	62	*R*

[a]Reactions at 1 mmol scale at −10°C in 5 ml of toluene. Reaction time 2–6 h. Conversion to the 1,4-product >95% (based on GC analysis). Isolated yields >70%. [b]Enantiomeric excess of **4** was determined by derivatization with enantiomerically pure 1,2-diphenylethylene diamine.[15] [c]Comparison of the specific rotation of **4** with known data gave the absolute configuration.[17]

General procedure for the synthesis of thiazolidinones 2

A mixture of the (*R*)-α-mercapto acid (10 mmol), the aldehyde (10 mmol) and aniline (0.93 g, 10 mmol) was azeotropically refluxed in 100 ml benzene in a Dean–Stark apparatus overnight. After cooling, the solution was evaporated to dryness to give a quantitative yield of crude **2** as a mixture of diastereomers. The diastereomeric excess of crude **2** was determined by 200 MHz ^{1}H-NMR (the absorptions of the thioacetal proton were used to determine the ratio). Diastereomerically pure material (*cis*) was obtained after recrystallization as indicated.

(2S,5R)-5-Methyl-3-phenyl-2-pyridin-2-yl-thiazolidin-4-one cis-***2a***

From **1a**, aniline and 2-pyridinecarboxaldehyde crude **2a** (d.e. 91%) was obtained. This material was recrystallized from EtOH to give diastereomerically pure *cis*-**2a** (1.84 g, 6.81 mmol, 68%) as glistening needles; mp 204.8–205.2°C; $[\alpha]_D$ +287.0 (*c* 1.03, $CHCl_3$); ^{1}H NMR δ 1.65 (d, *J*=7.0 Hz, 3H), 4.31 (q, *J*=7.0 Hz, 1H), 6.03 (s, 1H), 7.12–7.31 (m, 8H), 7.59–7.68 (m, 1H), 8.56 (d, *J*=4.4 Hz, 1H); ^{13}C NMR δ 18.22 (q), 41.28 (d), 63.95 (d), 120.08 (d), 123.21 (d), 124.52 (d), 126.61 (d), 129.03 (d), 137.15 (d), 149.97 (d), 159.31 (s); Anal. Calcd. for $C_{15}H_{14}N_2OS$: C, 66.64; H, 5.22; N, 10.36; S, 11.86. Found: C, 66.64; H, 5.14; N, 10.21; S, 11.71.

(2S,5R)-5-Methyl-3-phenyl-2-(6-methyl-pyridin-2-yl)-thiazolidin-4-one cis-***2b***

From **1a**, aniline and 6-methyl-2-pyridinecarboxaldehyde crude **2b** (d.e. 51%) was obtained. This material was recrystallized from ether/hexane to give diastereomerically pure *cis*-**2b** (1.54 g, 5.4 mmol, 54%); mp 110.5–112.3°C; $[\alpha]_D$ +161.5 (*c* 1.20, $CHCl_3$); ^{1}H NMR δ 1.64 (d, *J*=7.1 Hz, 3H), 2.53 (s, 3H), 4.30 (q, *J*=7.1 Hz, 1H), 5.98 (s, 1H), 6.97–7.55 (m, 8H); ^{13}C NMR δ 17.99 (q), 24.21 (q), 41.13 (d), 63.97 (d), 116.67 (d), 122.80 (d), 124.43 (d), 126.50 (d), 128.99 (d), 137.31 (d), 138.13 (s), 158.87 (s); Anal. Calcd. for $C_{16}H_{16}N_2OS$: C, 67.58; H, 5.67; N, 9.85; S, 1.27. Found: C, 67.36; H, 5.69; N, 9.81; S, 11.18.

(2S,5R)-5-Methyl-3-phenyl-2-quinolin-2-yl-thiazolidin-4-one cis-***2c***

From **1a**, aniline and 2-quinolinecarboxaldehyde crude **2c** (d.e. 24%) was obtained. This material was recrystallized four times from EtOH to give *cis*-**2c** (697 mg, 2.17 mmol, 22%, d.e. 94%) as glistening plates; mp 179.8–180.5°C; $[\alpha]_D$ +327.9 (*c* 1.20, $CHCl_3$); ^{1}H NMR δ 1.70 (d, *J*=7.1 Hz, 3H), 4.33 (dq, *J*=7.1 Hz and *J*=1.2 Hz, 1H), 6.25 (d, *J*=1.2 Hz, 1H), 7.08–8.17 (m, 11H); ^{13}C NMR δ 18.59 (q), 41.44 (d), 64.46 (d), 117.66 (d), 124.62 (d), 126.67 (d), 126.93 (d), 127.57 (d), 129.05 (d), 129.30 (d), 130.01 (d), 137.82 (d), 137.98 (s), 147.43 (s), 159.33 (s), 174.03 (s).

(2S,5R)-5-Isopropyl-3-phenyl-2-pyridin-2-yl-thiazolidin-4-one cis-**2d**

Starting from 9.5 mmol (*R*)-2-mercapto-3-methylbutanoic acid **1b**,[14] aniline and 2-pyridinecarboxaldehyde crude **2d** (d.e. 85%) was obtained. This material was recrystallized from EtOH to give diastereomerically pure *cis*-**2d** (1.09 g, 3.66 mmol, 39%) as a white powder; mp 119.6–120.9°C; $[\alpha]_D$ +292.2 (*c* 0.51, $CHCl_3$); ^{1}H-NMR δ 1.08 (dd, *J*=7.0 and *J*=6.6 Hz, 6H), 2.62 (m, 1H), 4.30 (s, 1H), 6.09 (s, 1H), 7.12–7.27 (m, 7H), 7.61 (m, 1H), 8.50 (m, 1H); ^{13}C-NMR δ 20.96 (q), 30.99 (d), 55.09 (d), 64.83 (d), 120.62 (d), 123.13 (d), 124.81 (d), 126.61 (d), 128.91 (d), 137.03 (d), 149.52 (d), CO and quartenary C not observed.

Conjugate addition of diethylzinc to cyclohexenone 3 and chalcone using catalytic amounts of $(CuOTf)_2$·benzene and chiral thiazolidinones 2

This procedure is typical for all conjugate addition reactions. A solution of $(CuOTf)_2$·benzene (5 mol%) and of chiral thiazolidinone (11 mol%) in 5 ml of toluene and 2 ml of CH_2Cl_2 was stirred at ambient temperature for 1 h under argon. A clear solution was formed. Substrate was added (1.0–2.0 mmol), the mixture was cooled to −20°C and diethylzinc in toluene (1.1 M, 1.5 equivalent) was added. Stirring was continued at −10°C for 2–6 h. An aliquot of the solution (0.1 ml) was taken and quenched with 1 ml of aqueous 1 N HCl. After extraction with 1 ml of diethyl ether the conversion was determined by GC analysis.[18] In all cases complete conversion was achieved with regioselectivities for the 1,4-product of >95%. The mixture was poured into 25 ml of aqueous 1 N HCl and extracted with diethyl ether (3×20 ml). The combined organic layers were washed with brine (25 ml), dried ($MgSO_4$), filtered and evaporated to give the crude 1,4-product. After purification by column chromatography (SiO_2, hexane:diethyl ether 5:1) the e.e.'s were determined.[18]

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